CBER DMPQ CMC/Facility BLA Review Memorandum

BLA STN 125771/0

Product Name [BIVV001/Altuviiio/efanesoctocog alfa]

Greg Price/Biologist/DMPQ/B3

1. BLA#: STN 125771/0

2. APPLICANT NAME AND LICENSE NUMBER

Bioverativ Therapeutics Inc., License # 2078

3. PRODUCT NAME/PRODUCT TYPE

BIVV001/Altuviiio/efanesoctocog alfa

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

a. Pharmacological category
Recombinant factor VIII replacement product

b. Dosage form
Lyophilized powder for reconstitution

c. Strength/Potency
250, 500, 750, 1000, 2000, 3000, and 4000 IU/vial

d. Route of administration
Intravenous

e. Indication(s)
Treatment of Hemophilia A

5. MAJOR MILESTONES

Filing meeting: August 17, 2022
Mid-Cycle Communication: October 30, 2022
PLI Inspection: December 5 – 9, 2022
Late-Cycle Meeting: January 17, 2023
Action Due Date: February 28, 2023

6. DMPQ CMC/FACILITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Greg Price, OCBQ/DMPQ/MRB3	Drug Substance, Drug Product, Facilities and CMC Reviewer and Lead Inspector
Alifiya Ghadiali, OCBQ/DMPQ/MRB1MRB3	Inspector

Prajakta Varadkar, OCBQ/DMPQ/MRB1MRB3	Inspector

7. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
6/30/2022	STN 125771/0.1	CMC and Facilities Information
8/17/2022	Amendment STN 125771/0.3 (Response to IR #1)	IR requesting previous equipment, manufacturing room qualifications, and DP sterilization validation reports
9/6/2022	Amendment STN 125771/0.6 (Response to IR #2)	IR regarding DP Line (b) (inspection readiness and manufacturing schedule
10/6/2022	Amendment STN 125771/0.10 (Response to PLI timeframe IR)	IR response to update manufacturing schedule for PLI
1/25/2023	Amendment STN 125771/0.26 (Response to shipping IR)	IR response to providing shipping validation documents
1/27/2023	Amendment STN 125771/0.28 (Response to CP facility information)	IR response providing facility information for the (b) (4) facility mentioned in CP as a new DP manufacturer
2/10/2023	Amendment STN 125771/0.34	IR response providing confirmation following successful completion of the CP it will be submitted as a PAS
2/13/2023	Amendment STN 125771/0.35	IR response providing BIVV001 (b) (4) container closure cleaning and sterilization validations

8. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Bioverativ Therapeutics Inc. is requesting approval for ALTUVIIIO (efanesoctocog alfa; referred to as BIVV001 by Bioverativ), an antihemophilic (recombinant), FC-von Willebrand factor-XTEN fusion protein, for the treatment of adults and children with Hemophilia A (congenital Factor VIII deficiency).

BIVV001 (b) (4) is expressed by human embryonic kidney (HEK) cells and produced in vitro using standard mammalian cell culture methods followed by chromatographic purification. BIVV001 drug product (DP) is a sterile, lyophilized powder for reconstitution for intravenous injection. The DP is supplied in aseptically filled single-use vials in seven nominal strengths of 250 IU, 500 IU, 750 IU, 1000 IU, 200 IU, 3000 IU and 4000 IU/vial. The composition of the formulation excipients prior to lyophilization is the same for all dosage strengths, only the quantity of BIVV001 varies. Sterile water for injection (sWFI) supplied in a prefilled syringe (PFS) is included with the lyophilized DP in the final package. The lyophilized DP is reconstituted with the sWFI pre-filled syringe (PFS) (nominal 3mL volume) using a sterile vial adapter (also supplied) prior to dosing.

The BIVV001 DS is manufactured at (b) (4) located in (b) (4) (b) (4) The (b) (4) BIVV001 DS CMC data and facility information were reviewed as part of this submission and the information was determined to be acceptable. The major manufacturing equipment and rooms used for BIVV001 manufacture are existing and have been approved for other FDA-approved products. In addition, (b) (4) has an acceptable FDA-inspection history and currently manufactures other FDA-approved recombinant antihemophilic factors for Bioverativ (b) (4) Aprolix [STN 125444]). For these reasons the decision was made to waive a pre-licensing inspection (PLI) of (b) (4) The data for (b) (4) (b) (4) BIVV001 DS manufacturing and facility information provided with this submission appears acceptable.

The BIVV001 DP is manufactured at the (b) (4) located in (b) (4) At (b) (4) the (b) (4) DP then transported to filling Line (b) (4) where it is sterile filtered, filled into vials, lyophilized, and capped via an automated process. A PLI of (b) (4) was conducted from (b) (4) (b) (4) quality systems, BIVV001 DP manufacturing, facilities, and QC laboratories were reviewed and determined to be acceptable.

The sWFI used to reconstitute the lyophilized BIVV001 DP is manufactured as a terminally sterilized PFS at (b) (4) (b) (4) (b) (4) has an acceptable FDA-inspection history and currently manufactures a similar terminally sterilized sWFI PFS for Bioverativ's FDA-approved product (b) (4) For these reasons the decision was made to waive a pre-licensing inspection (PLI) of (b) (4) The data for (b) (4) sWFI manufacturing and facility information provided with this submission appears acceptable.

B. RECOMMENDATION[1]

I. APPROVAL

Based on the information provided approval is recommended.

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Gregory Price, Biologist, OCBQ/DMPQ/MRB3	Concur	
CDR Donald Ertel, Branch Chief, OCBQ/DMPQ/MRB3	Concur	
Carolyn Renshaw, Division Director, OCBQ/DMPQ	Concur	

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[1] The review recommendations as indicated by the reviewer's signature for the CTD sections/subject matter is identified in section 6.

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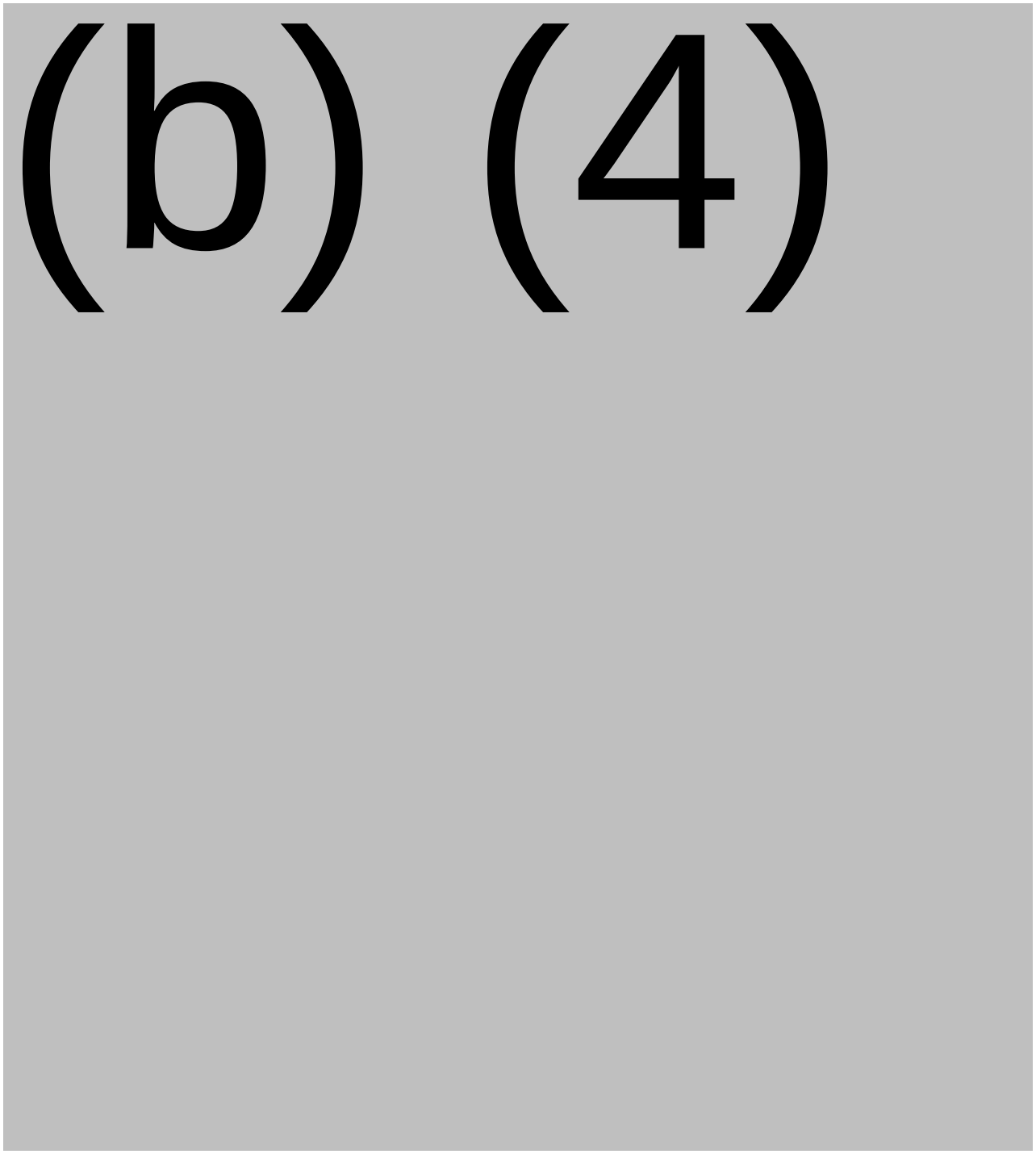
Module 3

3.2.S DRUG SUBSTANCE

(b) (4)

8 pages have been determined to be not releasable: (b)(4)



3.2.P DRUG PRODUCT
3.2.P.1 Description and Composition of the Drug Product

BIVV001 DP is a sterile, lyophilized powder for reconstitution for intravenous injection. It is supplied in aseptically filled single-use vials in seven nominal strengths 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU and 4000 IU/vial. The composition of the formulation excipients prior to lyophilization is the same for all dosage strengths and only the quantity of BIVV001 varies. The powder for injection is reconstituted with

sterile water for injection (sWFI) supplied in a prefilled syringe at a nominal volume of 3 mL. A vial adapter is also provided with the drug product vial (510(k) number (b) (4)) and the sWFI prefilled syringe to facilitate the administration.

The BIVV001 DP is filled into (b) (4) clear glass vials which are stoppered with 20 mm (b) (4) chlorobutyl rubber stoppers, (b) (4) and sealed with 20 mm colored aluminum seals with (b) (4) A different color cap is used per each dosage strength. The prefilled syringe is made of a (b) (4) (b) (4) glass syringe barrel with a bromobutyl rubber plunger stopper and tamper proof tip cap. The vial adapter 20 mm female Luer lock w/5µm filter is provided for reconstitution of the drug product.

3.2.P.2.5 Microbiological Attributes

Sterility of the lyophilized DP in vials is assured by sterile filtration directly followed by aseptic filling into the primary container closure. Sterility and endotoxin measurements are part of the release testing of the drug product.

Maintenance of the container closure integrity, and thereby sterility, is checked as part of the manufacturing process and during the shelf life of the drug product by container closure integrity testing. In addition, the potential impact of product shipment has been evaluated.

To assess integrity of the product after production and during storage, container closure integrity testing (CCIT) by (b) (4) or by (b) (4) is performed. The methods allow the detection of leaks (b) (4) and (b) (4) for the (b) (4) respectively. After filling and closing the vials CCIT is routinely conducted on samples of vials of each batch at (b) (4)

Reviewer Assessment
Note, the (b) (4) is no longer used for CCIT, which was used for the clinical batches. During the PLI, (b) (4) informed us the (b) (4) was used for the PV batches and will be used for all future batches. The validation of the (b) (4) CCIT method is reviewed in the CCIT section of this memo. The information provided appears acceptable and will be described in more detail below.

3.2.P.3 Manufacture
3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities.

3.2.P.3.3 Description of Manufacturing Process

The manufacture of the lyophilized DP is conducted in 10 distinct steps for all batch presentations (250IU, 500IU, 750IU, 1000IU, 2000IU, 3000IU, and 4000IU) and are presented below.

2 pages have been determine to be not releasable: (b)(4)

(b) (4)

Vials are labeled with an expiration date and lot number on each label. It is confirmed that both the correct expiration date and lot number are printed. Vials may be labeled prior to completion of release testing.

The labeled vials and leaflet are assembled in a unit carton. All cartons are printed with a lot number and expiration date.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- The manufacturing steps along with process descriptions were provided in this section. An open manipulation procedure occurs at (b) (4) where the bottles of (b) (4) This step was observed during the (b) (4) PLI and determined to be acceptable for the following reasons:
  - (b) (4)

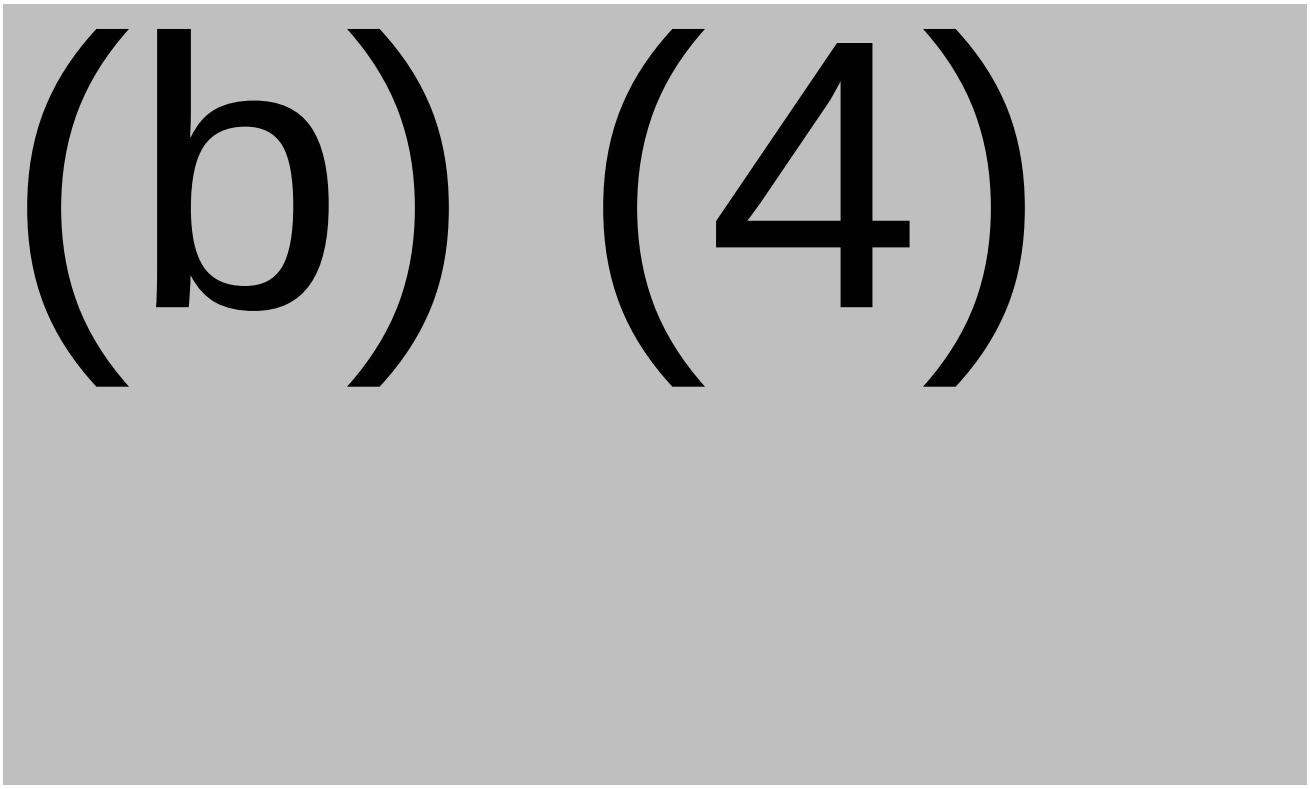
  The information provided appears acceptable.

3.2.P.3.4 Controls of Critical Steps and Intermediates

The in-process testing program encompasses the multiple manufacturing steps to ensure control of the manufacturing process. The testing classifications are listed as follows:

- IPCs are tests or on-line measurements that are performed during processing that allow decisions to be made regarding the operation of the process or the progression to the next processing step. IPCs have action limits.
- Critical IPC are in process testing at process steps directly controlled by acceptance criteria to ensure the desired product quality.
- In-process tests (IPT) are an output parameter used to assess process consistency and process performance in which results are evaluated after batch or processing step completion. IPTs are not used for real time process decision-making. IPTs have action limits.
- Critical IPT are in process testing at process steps directly controlled by acceptance criteria to ensure the desired product quality.

Bioburden and endotoxin are measured at multiple steps in the manufacturing train which are presented below:



Review of the remaining in-process tests are deferred to OTAT.

The process parameters are divided into either CCPs or KCPs. There are no bioburden or endotoxin process parameters, and we therefore defer review to OTAT.

Overall Reviewer's Assessment of Section 3.2.P.3.4:

- Bioburden and endotoxin are monitored at multiple steps in the manufacturing process. In addition, filter integrity is also measured to ensure product safety. The information provided appears acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

The process validation (PV) of BIVV001 DP was executed between (b) (4) (b) (4) which consisted of (b) (4) batches manufactured at variable batch size ranging from (b) (4) producing batch sizes of between approximately (b) (4) (minimum) and (b) (4) (maximum) vials. For the PV (b) (4) batches were manufactured at varying strengths. Information regarding these batches is presented below.

(b) (4)

2 pages have been determined to be not releasable: (b)(4)

(b) (4)

Aseptic Process Simulations

Aseptic process simulations (APS) for (b) (4) were submitted for 2021 and early spring of 2022. These were performed without any failures. However, because of the (b) (4) (b) (4) new APS runs were successfully completed. These were reviewed during the (b) (4) and were determined to be acceptable.

DP Shipping Validation

Bioverativ provided an operational qualification (OQ) simulated shipping validation report for (b) (4) drug product:

- Final Report for the Operational Qualification (OQ) for the Simulated Transport of (b) (4) BIVV001 (b) (4) Drug Product (study # 64-0090)

(b) (4)

3 pages have been determined to be not releasable: (b)(4)

(b) (4)

3.2.P.5 Control of Drug Product
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

(b) (4)

Reviewer Assessment
These are compendial tests. The information provided appears acceptable.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

(b) (4)

(b) (4)

Sterility
This section is deferred to DBSQC.

Reviewer Assessment
The (b) (4) for CCI was validated on BIVV001 DP vials and is sensitive enough to detect (b) (4) defects (b) (4) of the time. The sterility test is deferred to DBSQC. The information provided appears acceptable.

3.2.P.5.4 Batch Analyses

There have been (b) (4) clinical and/or stability batches manufactured prior to the (b) (PPQ manufactured at (b) (4) For these batches sterility and endotoxin were measured for each batch according to the specifications listed in the sections above. For all (b) (4) batches there have been no sterility or endotoxin failures.

Overall Reviewer's Assessment of Sections 3.2.P.5.4:
- No sterility or endotoxin failures for (b) (4) batches. The information provided appears acceptable.

3.2.P.7 Container Closure System

The BIVV001 drug product is lyophilized in the same (b) (4) (b) (4) glass vial for all dosage forms. Vials are closed with a 20 mm chlorobutyl rubber stopper, coated with (b) (4) on the product contact and top surfaces, with a cross-linked silicone oil treatment on the non-coated areas. After the lyophilization process is complete, the stoppered vials are sealed with 20 mm aluminum seals with a polypropylene (b) (4) . A distinct seal color is assigned to each nominal vial strength. Vial, stopper, and seal materials of construction and dimensions were presented in the submission.

The vials are washed, and a final rinse is performed with hot water for injection (WFI) (b) (4) at (b) (4) Following washing, the vials are (b) (4) (b) (4) The vials are transferred to the (b) (4) (b) (4) The glass vials are fed into the filling room from the (b) (4)

Stoppers are purchased washed (including a final rinse with water for injection) and ready to sterilize. The stoppers are lubricated using a (b) (4) which is a combination of high molecular weight silicones which are sprayed on the non-(b) (4)

coated areas of the stopper and are then (b) (4) to the surface of the stopper. The stoppers are sterilized using a (b) (4) The final step of the sterilization process includes a drying step, during which the stoppers are dried using a validated drying cycle.

Seals are purchased sterilized (by (b) (4)) or ready to sterilize. Seals are sterilized using a (b) (4)

Overall Reviewer's Assessment of Section 3.2.P.7:

- Container closure details, material of construction, dimensions, were provided. The information appears acceptable.

3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

Three stability studies are ongoing (primary, supportive, and confirmatory) for a duration of 48 months under normal storage conditions (5 ± 3°C), 12 months under accelerated conditions (b) (4) and 6 months under stress conditions (b) (4) CCIT is conducted at various timepoints for the normal and accelerated conditions. Sterility is not tested as this is part of release testing.

The primary stability study has been ongoing using DP batches made at (b) (4) (Dosage strengths 250, 500, 1000, 2000, 3000, 4000 IU/vial). Currently, 36 months of data are available for the normal storage conditions and the accelerated and stressed conditions have been completed. CCIT was conducted at the initial timepoint, 12, 24, and 36 months, with scheduled CCIT testing at 48 months. There were no CCI failures to date.

The supportive stability study has been ongoing using DP batches made at (b) (4) (b) (4) (all dosage strengths 250, 500, 750, 1000, 2000, 3000, 4000 IU/vial). Currently, 3 to 12 months of data are available for the normal and accelerated conditions (CCIT not performed under stressed conditions). CCIT was conducted at the initial timepoint, and 12 months for some lots (additional scheduled CCIT at 12, 24, 36, and 48 months). There were no CCI failures to date.

The confirmatory stability study is being conducted with the (b) (4) PPQ DP batches (dosage strengths 250, 1000, and 4000 IU/vial). Currently, there are 3 months of data available for the normal and accelerated conditions (CCIT not performed under stressed conditions). CCIT was conducted at the initial timepoint, and will be schedule at 12, 24, 36, and 48 months. There were no CCI failures to date.

We defer review of the remaining stability tests to OTAT.

Overall Reviewer's Assessment of Section 3.2.P.8.1:
- There have been no CCI failures to date. The information provided appears acceptable.

3.2.P DRUG PRODUCT (Sterile Water for Injection)
3.2.P.1 Description and Composition of the Drug Product

The solvent is sWFI filled in a 3.0 mL syringe format.

3.2.P.2.5 Microbiological Attributes

The sWFI is filled in a container closure system comprising a syringe barrel, a (b) (4) (b) (4) tamper-evident closure and a rubber stopper (two syringe barrel formats with the same stopper and (b) (4)).

Manufacture of the sWFI PFS consists of (b) (4) (b) (4) The manufacturing process is controlled by in-process testing for bioburden (total viable count) in accordance with (b) (4) (b) (4) The terminal sterilization process is fully validated, both with respect to technical/physical characteristics and to microbiological challenge experiments. The sterilization cycle generates a (b) (4) overkill sterilization of the product.

To control the microbial attributes at release and during shelf life of the sWFI PFS, sterility and bacterial endotoxins testing are performed in accordance with (b) (4) (b) (4)

During development, the integrity of the container closure system was confirmed by conducting CCI testing. CCI for the sWFI PFS was confirmed as part of the process validation study in 2008 and in stability studies throughout product shelf life.

Reviewer Assessment
The information provided appears acceptable.

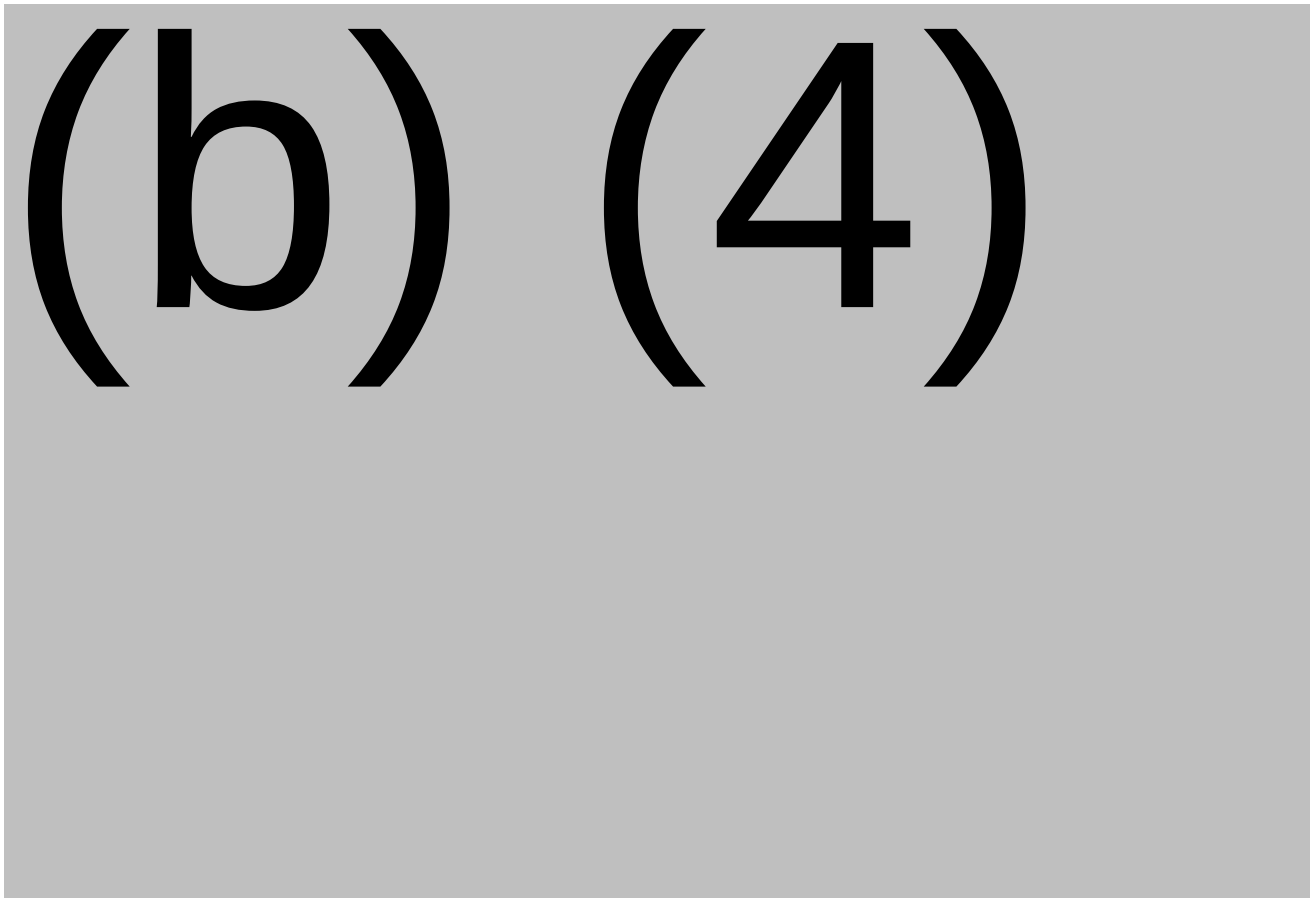
3.2.P.3 Manufacture
3.2.P.3.1 Manufacturer(s)

Refer to section 3.2.A.1 for a complete list of all manufacturing facilities

3.2.P.3.3 Description of Manufacturing Process

(b) (4)

1 page is determined to be not releasable: (b)(4)



3.2.P.3.4 Controls of Critical Steps and Intermediates

Bioburden measurement of filled syringes is one of the critical in process controls (CIPCs) measured following filling. The total viable count acceptance criteria for filled syringes is (b) (4)

The remaining CIPCs we defer review to OTAT.

Overall Reviewer's Assessment of Section 3.2.P.3.4:

- The filling of the syringes is a bioburden control process as the syringes undergo terminal sterilization following filling. The bioburden acceptance criterion maintains acceptable bioburden control. The information provided appears acceptable.

3.2.P.3.5 Process Validation and/or Evaluation

Validation for the manufacture of the 3.0 mL PFS was originally performed in (b) (4) and the process revalidated in (b) (4) following process improvements. These validations will not be reviewed here as (b) (4) manufactures a 3.0 mL sWFI (b) (4) FDA-approved product (b) (4)

(b) (4)

3.2.P.5 Control of Drug Product
3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

(b) (4)

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures (sWFI)

(b) (4)

(b) (4)

3.2.P.5.4 Batch Analyses (sWFI)

(b) (4) post approval batches of the 3 mL syringe were provided from years 2018 and 2020. Bacterial endotoxin (b) (4) and sterility (no growth) were measured. All testing passed acceptance criteria.

Overall Reviewer's Assessment of Sections 3.2.P.5.4
There were no endotoxin or sterility failures for the (b) (4) batches provided. The information appears acceptable. We defer evaluation of the remaining test results to OTAT.

3.2.P.7 Container Closure System (sWFI)

The description of the PFS components are as follows:

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.7:

- The components of the 3.0 mL PFS along with dimensions of the parts and certificates of analysis were provided in this section. The information provided is acceptable.

3.2.P.8 Stability
3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data (sWFI)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.8.1:

- All testing up to (b) (4) passed acceptance criteria for sterility, endotoxin, and CCI. The information provided appears acceptable.

3.2.A APPENDICES
3.2.A.1 Facilities and Equipment

There are three separate facilities that manufacture the BIVV001 (b) (4) lyophilized DP, and sWFI diluent. The review of each facility is described in the sections below. The facilities table listing all facilities involved in the manufacture, packaging, testing, and storage is provided in the facilities table below:

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
(b) (4)	Waiver	Yes	Yes	Last inspection (b) (4) performed by CDER (VAI)
	Inspection	Yes	Yes	Last two inspections (b) (4)

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
(b) (4)				performed by CDER (VAI) and PHRM2 (OAI)
	Not Required	No	Yes	
	Waiver	Yes	Yes	Last inspection (b) (4) performed by ORA (NAI)
	Not Required	No	Yes	
	Waiver	Yes	Yes	Last inspection (b) (4) performed by ORA (NAI)
	Waiver	Yes	Yes	Last inspection (b) (4)

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
(b) (4)				performed by ORA (NAI)
	Waiver	Yes	Yes	Last inspection performed (b) (4) by MRA and reviewed by ORA (VAI)
	Not Required	No	Yes	
	Waiver	Yes	Yes	Last inspection performed (b) (4) (b) (4) by ORA (NAI)
	Waiver	Yes	Yes	Last inspection performed (b) (4) by CDER (VAI)

Facility Manufacturing/ Testing activities	Inspection? Waiver? Not required?	Compliance check required for approval?	RMS-BLA entry required?	Comments
(b) (4)				
	Waiver	Yes	Yes	Last inspection performed (b) (4) by CDER (VAI)
	Not required	No	Yes	

Note, only (b) (4) facilities that are involved in DS, DP, and sWFI manufacture are reviewed here.

(b) (4)

6 pages are determined to not be releasable: (b)(4)

(b) (4)

Drug Product: (b) (4)
(b) (4)
A pre-license inspection (PLI) of the (b) (4) facility was conducted on (b) (4) (b) (4) The PLI was conducted to support BIVV001 DP manufacture on filling (b) (4) Filling (b) (4) is in (b) (4) and is physically segregated from the other filling line located in (b) (4) (b) (4) also contains visual inspection (VI), packaging, microbiology QC, warehouse, and mechanical areas in support of BIVV001 DP manufacture. It should be noted, (b) (4) is approved for the manufacture of two additional FDA-approved products, (b) (4) and (b) (4) In addition, no new manufacturing clean rooms, equipment, or utilities are being utilized for BIVV001 DP manufacture.

HVAC
The HVAC design criteria and method of operation are to provide and maintain temperature control, dehumidification, and room pressurization. (b) (4) are protected from cross contamination as 100% of the air from the filling, compounding and decontamination rooms is exhausted and there is no recirculation of air throughout manufacturing. Additionally, each line has its own dedicated HVAC system.

(b) (4) air handling units service (b) (4) air handling units serve the manufacturing areas, (b) (4)

The air handling systems serve areas with differing classifications: non-controlled unclassified space for office areas, and general use; controlled unclassified space for warehouse, packaging, and visual inspection areas; and classified space for manufacturing. Classified spaces are routinely monitored.

Reviewer Assessment
The information provided regarding the (b) (4) *HVAC systems appears acceptable. The HVAC systems and validation were also reviewed during the* (b) (4) *PLI and were determined to be acceptable. Environmental monitoring for the* (b) (4) *manufacturing areas is provided below.*

Clean Utilities
WFI
Source water for the feed water system is domestic water. Feed water is produced by reverse osmosis and electro-deionization. The water is stored in a (b) (4) tank and is pumped from this tank into a distribution system. Water not utilized is returned into the tank by the (b) (4)

For WFI, chemical and microbiological testing is performed per a defined schedule and according to (b) (4) requirements. (b) (4) This water is pumped into a distribution system with (b) (4) (b) (4) (b) (4) recirculate back to the WFI holding vessel. WFI (b) (4) is continuously recirculated and maintained at (b) (4) to ensure self-sanitizing conditions.

WFI is used for the lyophilizer (b) (4) cycle.

WFI is connected via process-dedicated sanitary hoses or hard piped connections to the equipment. Hoses are flushed (per internal procedure) prior to use. The WFI system operates at a higher pressure than the process and loss of WFI pressure is alarmed in the Parenteral Control System (ParCS), the automation control system in the (b) (4)

Clean Steam
Clean steam is used for steam sterilization of autoclave loads and lyophilizer chamber (b) (4) Clean steam is tested according to a defined schedule according to (b) (4) (b) (4) requirements.

Clean Steam is connected via process-dedicated (b) (4) (b) (4) to the equipment. The clean steam system operates at a higher pressure than the process and loss of clean steam pressure is alarmed in the ParCS.

Nitrogen

Nitrogen is used for moving fluids during filter integrity test operations, for pressuring vessels, for vacuum control and vacuum break within the lyophilizer. Nitrogen is tested per a defined schedule per (b) (4) requirements. Nitrogen is sterile filtered at the point of use.

Nitrogen is connected via process dedicated (b) (4) to the equipment. The nitrogen system operates at a higher pressure than the manufacturing process and loss of nitrogen pressure is alarmed in the ParCS.

Process Air

Process air is connected via process dedicated (b) (4) (b) (4) (b) (4) to the equipment. Process air is used for moving fluids during filter flush operations and on the load door inflatable gasket for the lyophilizer. The process air system operates at a higher pressure than the manufacturing process and loss of process air pressure is alarmed in the ParCS.

Reviewer Assessment

The information provided regarding the (b) (4) *clean utilities appears acceptable. The* (b) (4) *clean utilities and validations were also reviewed during the* (b) (4) (b) (4) *PLI along with annual and quarterly trend reports from year* (b) (4) *to* (b) (4) *and determined to be acceptable.*

Environmental Monitoring

An environmental monitoring program is in place that measures viable and non-viable particles during routine and medial fill simulations. For viable monitoring, (b) (4) Critical process flow and representative sites are monitored at the completion of the filling of the final batch of a campaign. (b) (4) are performed according to established procedures. Organisms detected in the (b) (4) are identified to the species level.

Viable air sampling is performed under dynamic conditions in the (b) (4) , (b) (4) area where the DP is filtered and filled in a (b) (4) (b) (4) areas are also routinely monitored. Viable active air sampling in the (b) (4) is performed using a qualified air sampler. In the (b) (4) air sampling is additionally performed with (b) (4) Monitoring levels are established in (b) (4) procedures for classified production areas and are set according to the requirements of the current version of Annex 1 of the EU Guide to Good Manufacturing Practice and USP and follow FDA guidance as listed in “Guidance for Industry Sterile Drug Products Produced by Aseptic Processing —Current Good Manufacturing Practice”.

Continuous non-viable particulate monitoring is performed at designated locations on (b) (4) during operation for the (b) (4) There is a small (b) (4) (b) (4) section for the transition from the (b) (4) to the (b) (4) (b) (4) non-viable particle monitoring is performed in the (b) (4) area in operation. Particle counts for particulates (b) (4) and (b) (4) are monitored.

Reviewer Assessment
The information provided regarding the EM program appears acceptable. The EM programs and qualification programs along with the quarterly trend reports from year 2020 to 2022 were reviewed during the (b) (4) *PLI and determined to be acceptable.*

Facility Cleaning
All manufacturing rooms for (b) (4) and (b) (4) are cleaned and sanitized based on established procedures with specified frequencies depending on the room classification. (b) (4) utilizes (b) (4) cleaning and sanitization solutions, (b) (4) and (b) (4)

All room floors in the facility are cleaned (b) (4) All external passthrough(s) and internal passthrough(s) are cleaned (b) (4) All material and gowning airlock floors are cleaned (b) (4) All rooms, including walls and floors, are cleaned (b) (4) All rooms, including ceilings, walls, and floors, are cleaned (b) (4). All room surfaces, including equipment surfaces, in the facility are cleaned (b) (4) or following (b) (4) activities.

Reviewer Assessment
Facility cleaning and disinfectant effectiveness studies were reviewed during the (b) (4) *PLI and determined to be acceptable. Refer to the EIR for additional information.*

BIVV001 DP Process Equipment Validation
All direct impact equipment used for manufacturing on (b) (4) has been fully validated. Equipment validation is comprised of the following activities:

1. Design, Installation, and Specification Confirmation (IC) – Verification of design criteria and installation, traditionally known as installation qualification (IQ).
2. Functional Confirmation (FC) – Verification that the equipment functions appropriately within the intended operational or design range. Sterilization cycles for specified equipment are confirmed at this stage of validation. This is traditionally known as operational qualification (OQ).
3. Operational Confirmation (OC) – Verification that the equipment operates as expected. Testing includes, but is not limited to, sterilization and depyrogenation, traditionally known as performance qualification (PQ).
4. Cleaning Validation – Verification that equipment can be cleaned to the specified level after manufacturing use. The BIVV001 filling process utilizes disposable, single-use components for processing, no cleaning validation is performed for the filling equipment. The lyophilizer is not dedicated and cleaning verification is used to confirm the removal of residue from the lyophilizer to an acceptable level.

Cleaning verification is performed (b) (4) of a product campaign. Cleaning verification is utilized until a validated cleaning process is in place.

Reviewer Assessment

As mentioned above, the major (b) (4) *BIVV001 processing equipment has been approved for other FDA-approved products,* (b) (4) *and* (b) (4) (b) (4) *Major BIVV001* (b) (4) *equipment qualifications or requalifications (where applicable) and equipment cleaning validations were reviewed during the* (b) (4) (b) (4) *PLI and determined to be acceptable. This included the vial washer, autoclave, depyrogenation tunnel, lyophiilizer, vial filler, capper, and isolator sanitization and decontamination. The information provided appears acceptable.*

Sterilization of Product Contact Equipment

(b) (4) pre-sterilized product contact equipment is utilized for the manufacture of products on (b) (4) at the (b) (4)

The filling assembly (dosing manifold in (b) (4) system) is supplied by (b) (4) (b) (4) a (b) (4) approved supplier, and is (b) (4) by (b) (4) provider, (b) (4) The vendor uses a product family approach in establishing sterilization validation parameters for its (b) (4) product line, which includes the (b) (4) dosing manifold. The product part number of (b) (4) was identified to be the worst case within that product family. Sterilization dose audits are repeated on a (b) (4) basis to demonstrate continued substantiation of sterilization dose.

The lyophilizer is sterilized utilizing a validated (b) (4) cycle. The (b) (4) cycle requires a minimum (b) (4) and thermocouple temperatures greater than (b) (4) for the entire exposure period. The performance is verified during validation utilizing thermocouples and biological indicators containing (b) (4) (b) (4) Biological Indicators (BIs) used for the validation of steam sterilization cycles must meet the following specification of (b) (4) with a population of (b) (4) and a (b) (4) The expected result during the validation of steam sterilization cycles is that all exposed BIs show no growth for (b) (4)

Reviewer Assessment

The information provided appears acceptable. Sterilization of product-contact equipment was also reviewed during the (b) (4) *PLI and determined to be acceptable*

Facility Controls Against Cross Contamination

A cross contamination risk assessment between (b) (4) and (b) (4) has been documented in a comprehensive assessment evaluating severity, probability of occurrence, and probability of detection of identified risks to facility procedures, equipment, and processes. Mitigations reaching a pre-defined moderate or high-risk scoring during evaluation have been completely mitigated to further decrease risk of

occurrence. The high-level controls that were put into place to accomplish this are the following:

- Engineering Controls
- Line Segregation
- Production Segregation and Controls
- Utility Systems Design Controls
- Material Flow/ Component Flow
- Personnel Segregation and Control

(b) (4) has a comprehensive approach to the prevention of cross contamination. These practices provide assurance that the risk of cross contamination between processes from (b) (4) and (b) (4) within the facility are effectively minimized. In addition, these practices ensure that Biogen operates in compliance with regulatory requirements and guidance.

Reviewer Assessment

The information provided appears acceptable. Facility controls to prevent cross-contamination were also reviewed during the (b) (4) *PLI and were determined to be acceptable.*

(b) (4)

Reviewer Assessment
The information provided appears acceptable. Product changeover methods were also reviewed during the (b) (4) *PLI and were determined to be acceptable.*

sWFI PFS: (b) (4)

The sWFI PFS is manufactured under contract by (b) (4) (b) (4) Manufacturing is performed at the (b) (4) cleanroom (b) (4) and associated areas.

The facilities used for the manufacture of the sWFI PFS are designed for multi-product operations and consist of (b) (4) The personnel and material flow within the facility is designed in a manner that contamination or errors are reduced to a minimum. The manufacturing areas feature air-handling systems providing an appropriate air quality for the intended operations. Rooms involved in manufacturing have proper air cascades and pressure differentials to facilitate the airflow from critical to less critical areas. Operations during which the product is exposed to the environment are performed under protected conditions under laminar airflow (LAF).

Surface finishes are made of impervious materials thus, making the surfaces easier to clean and maintain. Access to the whole production area is controlled. Personnel enter the production area through air locks. Gowning and personal sanitation standard operation procedures (SOPs) are in place and must be adhered to by all personnel entering the production area.

sWFI PFS Manufacturing Areas

(b) (4)

Reviewer Assessment
Flow diagrams and room classifications were provided in the submission. The information appears acceptable.

Major Equipment
Equipment used for compounding, filtration/sterile filtration and filling of the WFI that has direct contact with the product is either (b) (4)

(b) (4) The list of major equipment is provided below.

- Glass barrel washing machine
- Dry heat tunnel (depyrogenation/sterilization of syringes)
- Rubber part washing machines (washing and siliconization of stoppers)
- Autoclaves (Sterilization of compounding and filling equipment and terminal sterilization of sWFI PFS)
- Filling machine (filling of sWFI syringes)

Reviewer Assessment
Requalification documents of the washers, depyrogenation tunnel, and autoclaves were provided and reviewed under the process validation section. Note, product contact equipment is dedicated or single use. As the product is sWFI cleaning validations are not required. The information provided here appears acceptable.

Prevention of Contamination / Cross-Contamination / Mix-ups

HVAC System
The heating, ventilation, and air conditioning (HVAC) system provides conditioned air to the cleanroom areas. For air filtration, high efficiency particulate air (HEPA) filters with required efficiency are used. HEPA filters are included in an existing program for performance testing and maintenance. HEPA filters in LAF areas of cleanrooms are integrity tested on a regular basis. Laminar airflow units are alarmed.

Equipment Cleaning and Sterilization
All product contact equipment is cleaned and sterilized prior to use using validated CIP/SIP cycles.

Product Changeover
Line cleaning/line clearance is performed between different manufacturing batches to ensure that the manufacturing area is free of product and specific documents and equipment from the previous batch.

Line cleaning is performed (b) (4) Manufacturing lines and associated rooms are cleaned (b) (4) i.e., specific documents and equipment from (b) (4) line cleaning also includes cleaning procedures for manufacturing equipment and facilities.

Line clearance is performed (b) (4) It also includes the check of commonly used machines and equipment, e.g., autoclaves, ovens, washing machines, for cleanliness and operational readiness, the inspection of the manufacturing area regarding the absence of product and specific documents and equipment from the previous batch and with regard to cleanliness. The identity of all raw materials and the container closure system components is verified, and the release

status is checked prior to use. In addition, the identity and cleanliness status of equipment used for compounding, filtration and filling are verified and documented.

Personnel conducting line cleaning / line clearance procedures are properly trained. Any deviations occurring during line cleaning / line clearance are immediately addressed and properly evaluated and documented. The personnel are trained in procedures that prevent cross contamination, including proper gowning procedures, material and product flow, handling of product waste, etc.

Reviewer Assessment
Product-contact equipment is dedicated to sWFI or single-use. Line clearance and product changeover operations are in place. The information provided appears acceptable.

Environmental Monitoring
Viable Monitoring
Surfaces in the (b) (4) involved in the product manufacturing are monitored at established locations. (b) (4) are used on surfaces. For personnel, (b) (4) are used.

Surface monitoring is performed at the (b) (4) the manufacturing in (b) (4) areas. Surface monitoring in (b) (4) areas is performed (b) (4) during manufacturing. Personnel monitoring is conducted on defined locations (at least on hands).

(b) (4) areas are also monitored on a routine basis, both inside and outside the LAF protected areas. In the compounding areas, both the laminar-flow area and the surrounding (b) (4) area are monitored on a routine basis.

Germ identification on (b) (4) are performed according to established SOPs.

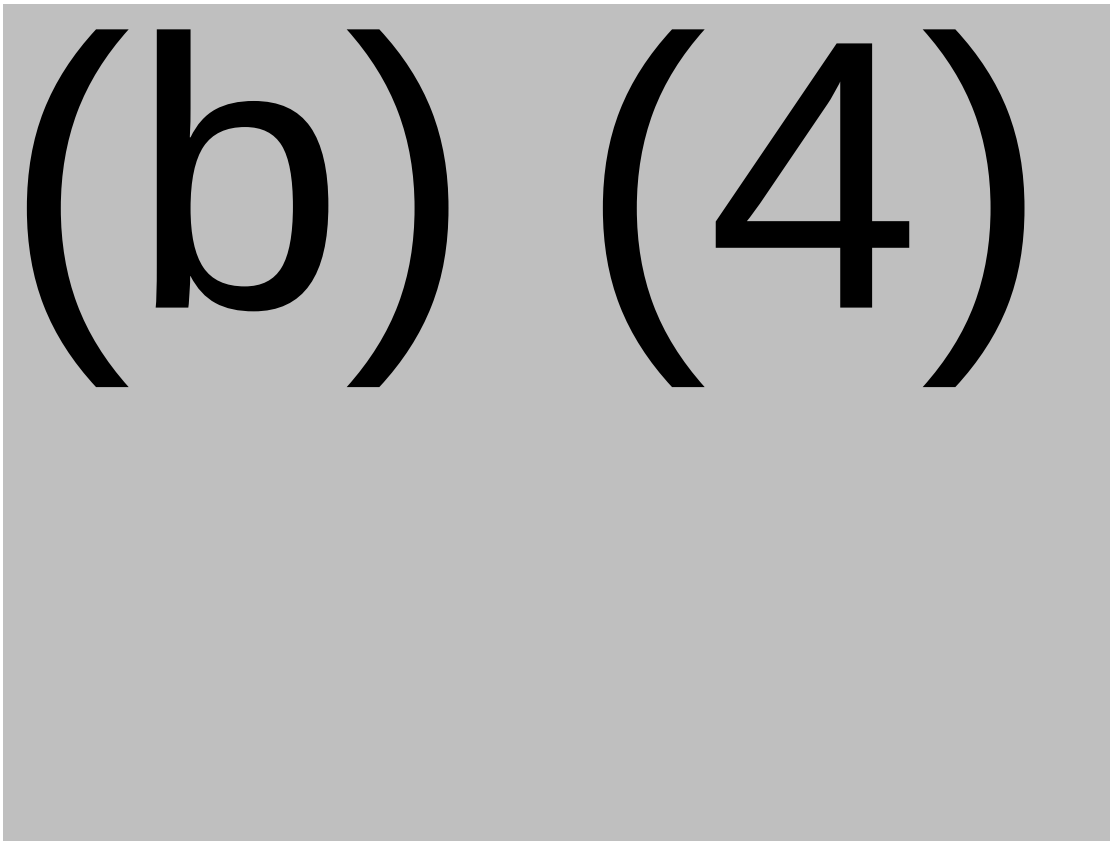
Viable air monitoring is performed in (b) (4) where the product is sterile filtered and filled, in the surrounding (b) (4) areas and (b) (4) areas on defined sampling points.

Active air sampling in (b) (4) and (b) (4) is performed via (b) (4) method. Each filter is exposed to (b) (4) of air. In (b) (4) areas air sampling is additionally performed with (b) (4) Active air monitoring is performed during setup in (b) (4) areas at defined regular intervals. In (b) (4) areas, active air monitoring is performed (b) (4)

(b) (4) areas are also monitored on a routine basis, both inside and outside the LAF protected areas.

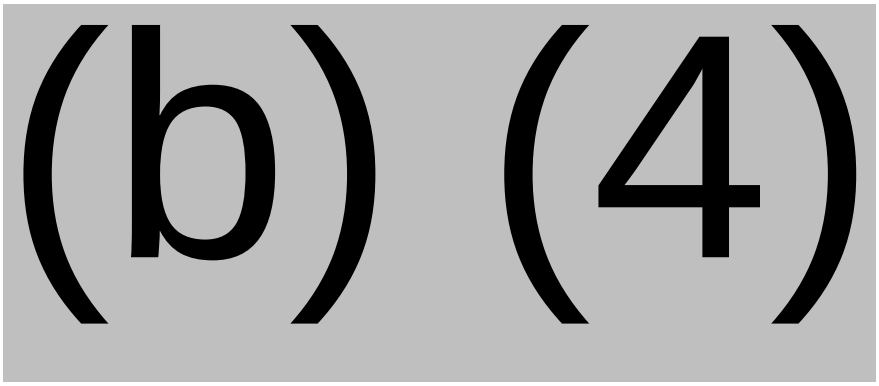
Germ identification on (b) (4) is performed according to established SOPs.

The following lists the current monitoring limits for classified production areas:



Non-viable Monitoring

Continuous non-viable particulate monitoring is performed at designated locations in (b) (4) and (b) (4) on (b) (4) during operations. In (b) (4) monitoring during operation takes place on a regular basis. The limits for non-viable particulate monitoring during operations are presented below.



Reviewer Assessment

Viable and non-viable environmental monitoring programs are in place with adequate stringency based on the FDA guidance document "Guidance for Industry Sterile Drug

Products Produced by Aseptic Processing —Current Good Manufacturing Practice". The information provided appears acceptable.

Clean Utilities

Purified Water (PW) and WFI

Source water for the PW system is potable and tested according to a defined schedule for e.g., (b) (4) PW is produced using (b) (4) The water is stored in (b) (4) tanks and (b) (4)

WFI is prepared from purified water by (b) (4) tanks. (b) (4) WFI is kept at (b) (4) and (b) (4) at this temperature to ensure sanitized conditions. Prior to dispensing, the WFI is passed through a (b) (4) (b) (4) to the required temperature.

Chemical and microbiological testing (e.g., microbial count, endotoxins, TOC, and conductivity) is performed on the PW and WFI systems according to a defined schedule and according to (b) (4) requirements. Alert and action limits are established for both.

Clean Steam

Clean steam is used for steam sterilization e.g., of autoclave loads and equipment. Clean steam is tested according to a defined schedule and according to (b) (4) (b) (4) requirements. Alert and action limits are established.

Compressed Air

Compressed air is plant generated and distributed throughout the plant using clean piping. Air is filtered through a central filter station (b) (4) and additionally at the point of use. Compressed air is chemically and microbiologically tested according to a defined schedule and according to (b) (4) requirements.

Nitrogen

Nitrogen is used for filtration and overlaying. Nitrogen is filtered through a central filter station (b) (4) and at the point of use. Nitrogen is chemically and microbiologically tested according to a defined schedule and according to (b) (4) requirements.

Reviewer Assessment

Chemical (as applicable) and microbial testing are in place for the clean utilities and based on compendial monitoring standards. The information provided appears acceptable.

Overall Reviewer's Assessment of Section 3.2.A.1:

- (b) (4) manufacture) has an acceptable inspection history with the FDA (see facility table above) and currently manufactures other FDA-approved recombinant coagulation factors for Bioverativ (b) (4) (b) (4) According to Bioverativ none of the equipment used to manufacture BIVV001 is new and is used to manufacture other FDA-approved products. In addition, none of the manufacturing rooms are new and the clean utilities remain unchanged. The information provided for the (b) (4) facility appears acceptable.

- A recent PLI in support of BIVV001 manufacture at (b) (4) (DP manufacture) was conducted by the FDA from (b) (4) (b) (4) quality systems, BIVV001 manufacturing, facilities, and QC laboratories were reviewed and determined to be acceptable. The information provided with this submission appears acceptable.

- (b) (4) (sWFI PFS manufacture) has an acceptable inspection history with the FDA (see facility table above) and currently manufactures a similar 3.0 mL sWFI PFS for another Bioverativ FDA-approved product, (b) (4) As this is not a new facility and not a new product for (b) (4) the information provided appears acceptable.

3.2.R Regional Information (USA)
Combination Products

Design control of the (b) (4) sWFI PFS
The sWFI PFS is supplied by (b) (4) and is a single-use syringe developed for dilution or reconstitution of various drug products. The syringes contain a minimum extractable volume (MEV) of sWFI between (b) (4) and (b) (4) in two different syringe formats ((b) (4) and (b) (4), differing only in the length of the syringe), with each syringe format comprising the same container closure (i.e., rubber stopper and tamper-evident seal).

The development of the sWFI PFS by (b) (4) occurred before the requirements for combination products according to the FDA Guidance for Industry and Food and Drug Administration Staff, "Current Good Manufacturing Practice Requirements for Combination Products" became effective. Retrospective design control activities have been performed to fulfill the requirements of CFR 820.30 Design Controls for the design of the PFS.

Design plan
A design plan was issued which summarizes the product description and the intended use for dilution and reconstitution of various drug products.

Design input

The design input requirements were established in terms of the intended use for dilution and reconstitution of various drug products considering the sWFI PFS in its closed configuration.

The following aspects have been addressed for the design input of the sWFI PFS:

- Design requirements
- Functional requirements
- Regulatory requirements
- Durability requirements
- Storage requirements

These design aspects are captured in the alignment of design input requirements with user requirements which is included in (b) (4) design history file.

Design output

Design outputs were developed to enable conformance to the design input requirements. The final design output consists of the following:

- Functional requirements of the sWFI PFS
- Quality control aspects including the following:
  - Dimension and quality of primary packaging components
  - Container Closure Integrity (CCI)
  - Break-loose and gliding forces (BLGF)
  - Extractable volume/Volume in container
- Storage condition and shelf life

Design Verification

Design verification comprising Luer connectivity and functional capability of the sWFI PFS has been performed considering the FDA draft Guidance "Glass Syringes for Delivering Drug and Biological Products: Technical Information to Supplement International Organization for Standardization (ISO) Standard 11040-4". Testing was performed on the commercial design configuration and covers a shelf life of (b) (4) under long-term storage conditions of (b) (4) and (b) (4) (b) (4) All data obtained throughout (b) (4) were in line with the defined specification.

Luer connectivity tests were performed with the (b) (4) syringe format filled with (b) (4) (b) (4) sWFI. Testing is applicable for both the (b) (4) and (b) (4) formats as luer connectivity of the sWFI PFS is not impacted by the filling volume nor by the syringe format as both formats differ only in the length of the syringe. The Luer connectivity testing performed with the sWFI PFS are the following:

- Fitting connection
- Seal integrity test to assess liquid leakage
- Seal integrity test to assess air leakage
- Separation force
- Unscrewing torque

- Resistance to Overriding
- Stress cracking

This testing was performed at the initial timepoint,(b) (4) of stability storage. Functional capability testing for tip cap removal force and piston seal blowback were performed with the (b) (4) syringe format filled with (b) (4) sWFI. Testing is applicable for both the (b) (4) and (b) (4) formats as these tests of the sWFI PFS are not impacted by the filling volume nor by the syringe format as both formats differ only in the length of the syringe. All testing at all timepoints passed acceptance criteria.

The functional capability tests performed for the sWFI PFS are the following:

- Tip cap removal force
- Piston seal blowback
- Seal integrity test to assess dye ingress (container closure integrity)
- Break-loose force
- Gliding force
- Extractable Volume/ Volume in container

Break-loose and glide forces have been tested during process validation as in-process control and after terminal sterilization for release. In addition, they are part of the control strategy and are performed as in process test during filling. Long-term suitability has been verified during the long-term stability study covering a shelf life of (b) (4)

Risk Management
During product lifecycle of the sWFI PFS, risk assessments are performed according to supplier procedures when needed and documented in the supplier's design history file.

Biocompatibility
Biological evaluation activities were performed on the PFS and vial adapter in accordance with ISO 10993-1 Biological evaluation of medical devices—Part 1: Evaluation and testing within a risk management process. Based on biocompatibility evaluation and results of the biocompatibility testing, the PFS is biocompatible for its intended use and the benefits outweigh the risks. All requirements of ISO 10993-1 were met. We defer review to OTAT.

Vial Adapter
An FDA 510(k) Premarket Notification for the (b) (4)
VF was submitted [510(k) number (b) (4)

Compliance to 21 CFR Part 4 Section 820 Requirements
The BIVV001 DDCP has been classified by FDA as a co-packaged combination product. 21 CFR Part 4 clarifies the application of current good manufacturing practice regulations to combination products and provides a regulatory framework for designing

and implementing the current good manufacturing practice operating system at facilities that manufacture co-packaged or single combination products. This is documented in Report BIVV001_21CFRPart4 "Combination Product – Compliance Assessment to 21 CFR Part 4", provided in the submission in 3.2.R Regional section.

The report outlines the quality systems that satisfy the below listed provisions of the quality systems regulation. By demonstrating that these requirements are satisfied, there is no additional demonstration of compliance required with respect to the quality systems:

- Section 820.20 of this chapter Management responsibility
- Section 820.30 of this chapter Design controls
- Section 820.50 of this chapter Purchasing controls
- Section 820.100 of this chapter Corrective and preventive action
- Section 820.170 of this chapter Installation
- Section 820.200 of this chapter Servicing

Installation and Servicing are not applicable due to the nature of the products (disposable, single use injectable).

Overall Reviewer's Assessment of Combination Products Section:

- The (b) (4) 3.0 mL sWFI PFS has undergone the required design verification testing and Bioverativ appears to comply with 21 CFR Part 4 Section 820 requirements for their co-packaged product. The information provided is acceptable.

Comparability Protocols

A comparability protocol was included with this submission to add an alternate BIVV001 DP manufacturing facility, (b) (4) The objective of this comparability plan is to assess the comparability of the BIVV001 drug product manufactured at (b) (4) versus the BIVV001 drug product to be manufactured at (b) (4) based on the biochemical properties of drug product release and characterization testing. With the addition of (b) (4) as an alternate manufacturing site, manufacturing changes are proposed. These include an (b) (4) of scale of production to support future supply for BIVV001 DP and changes to the overall manufacturing process, to enable (b) (4) scale batches and to suit (b) (4) fill-finish site capabilities. Also proposed is a change to the vial from (b) (4) vial to (b) (4) vial.

Vial Change

The new vial, referred to as (b) (4) vial, is the same (b) (4) vial as at (b) (4) except it has an internal hydrophobic silicone coating. The (b) (4) vial was selected to mitigate fogging effect based on the results obtained from the development studies performed at (b) (4) and (b) (4) There are no other changes to the container closure system such as stoppers and seals.

Process Equipment Changes

(b) (4)

Fill Finish Process Changes

(b) (4)

(b) (4)

Risk Assessment

A risk assessment was presented to examine the overall risk due to the equipment and process changes. To mitigate these risks Bioverativ will conduct developmental studies, and/or engineering runs and PPQ batches. Extractable/leachable studies will be conducted for the vial, filter, and new product contact materials.

Comparability Approach

To confirm no adverse impact to quality due to changes and to establish comparability between manufacturing sites, the following comparability approach will be applied to both engineering and PPQ runs.

- BIVV001 DP results from (b) (4) will be compared against the release specification and to historical data generated for BIVV001 at (b) (4) Comparability acceptance criteria will be established by statistical analysis of historical data for relevant CQAs to show DP is comparable.
- BIVV001 DP characterization data will be generated to gain product knowledge and understanding. Where applicable characterization data will be compared to historical data sets generated during development on (b) (4) batches.
- The analytical package to support the comparability has been chosen to maximize the potential for detecting relevant differences in the quality attributes of the drug product including, biological activity, Purity, Impurities, and Contaminants.
- Stability data under stress conditions will be used to support the comparability assessment.
    - (b) (4) DP batch manufactured at (b) (4) will be compared to (b) (4) DP PPQ batch at (b) (4) under stress conditions (b) (4) for stability-indicating release tests.

These studies will have protocols with pre-defined acceptance criteria for successful execution described within, and each study will have an associated report describing the results. Overall success of the comparability protocol will be determined by the outcome of all these studies and will be discussed in a comparability report issued by (b) (4)

Data To Be Reported

A comparability report plus supportive data will be submitted to the Agency in the post-approval change filing. The comparability report will compile all the pieces of information gathered and will include at least:

- The description of DP lots involved in the comparability exercise,
- The description of the comparability work conducted, in agreement with the indications in this comparability plan.

- All testing results
- Specifications and acceptance criteria.
- The assessment of all testing results in comparison with the acceptance criteria or action limits.
- Any deviations detected and investigated.
- 3-months stability data under long-term and accelerated storage conditions on the PPQ batches.

Propose Reporting Category
The proposed reporting strategy for this change is Change Being Effected (CBE) 30.

Reviewer Comments to CP
Bioverativ provided almost no information regarding the proposed facility. To obtain more information regarding facilities an IR was submitted to Bioverativ on January 20, 2023, and the response was received on January 27, 2023 (eCTD # 28).

Bioverativ Response
Bioverativ provided the FEI number and address of the DP facility in question which is listed below:

- (b) (4)

Review of OSAR indicates the (b) (4) *facility has an acceptable inspection history. The most recent FDA-led inspection was in* (b) (4) *and was classified as voluntary action indicated (VAI). A Mutual Recognition Agreement (MRA) comprehensive GMP inspections was conducted by the* (b) (4) (b) (4) *which was classified as VAI.*

Bioverativ also provided general facility and equipment information. The (b) (4) *facility contains two integrated fill/finish lines with BIVV001 to be process on Fill Finish* (b) (4) *Fill* (b) (4) *is enclosed within a* (b) (4) *isolator and an EM program is in place. Filling* (b) (4) *has two qualified and operational lyophilizers installed.*

BIVV001 Manufacturing Equipment
Bioverativ provided a list of all major equipment to be used for BIVV001 manufacture and whether it is used for other FDA-approved products. The majority of the equipment is used for FDA-approved products except the following:

(b) (4)

For the above new equipment qualification protocols are in place and qualification testing has been completed, under execution, or testing results under review for approval.

BIVV001 Manufacturing Equipment Cleaning
Product-contact equipment will consist of single-use technology or stainless steel. BIVV001 is not considered worst-case soil and therefore (b) (4) *confirmatory CV run will be completed for each piece of product-contact equipment. The cleaning validation protocol will be executed in parallel with PPQ runs. The CV protocol testing rationale will address the following:*

- *Matrixing approach*
- *Chemical and Micro* (b) (4) *endotoxin & bioburden) testing and the associated acceptance criteria.*
- *Equipment grouping / family grouping*
- *Equipment product contact surfaces and materials of construction*
- *Dirty hold times (product specific)*

BIVV001 Production Rooms
All proposed BIVV001 manufacturing rooms are existing spaces and have been qualified for other FDA-approved products except for the (b) (4) *following rooms which are new:*

- (b) (4)

List of new facilities/utilities qualification data to be submitted with executed CP
Bioverativ provided a list of new facilities/utilities related qualifications implemented to manufacture BIVV001 which are listed below:

- *WFI POU (Performance Qualification Protocol Report for WFI in Fill Finish* (b) (4)
- *HVAC (Installation and Operation (IOQ) Report for the* (b) (4) (b) (4)
- *Formulation Suite and associated personnel and materials airlocks (Performance Qualification Report for Environmental Monitoring of* (b) (4) (b) (4) *)*

Container Closure Integrity Test (CCIT) Validation for BIVV001 DP at (b) (4)
The current submitted method for Container Closure Integrity Test (CCIT) method ((b) (4) *) performed by* (b) (4) *will not be transferred to* (b) (4) *Instead, a Container Closure Integrity Test (CCIT) method using* (b) (4) *will be validated for use for testing BIVV001 drug product at* (b) (4) *This method has not yet been evaluated by CBER but has been evaluated and approved by CDER for use in the products listed below.*

- (b) (4)

: (b) (4)

The (b) (4) *method will be used for* (b) (4) *analysis where* (b) (4) *content is measured, and breach of container closure is indicated by* (b) (4) *ingress. Correlation between* (b) (4) *ingress and container breach sizes down to* (b) (4) *will be assessed.*

Previous validation work on the above products has shown that (b) (4) *ingress in the vial is impacted by the vial size and as such, additional validation studies will be performed for the container used for BIVV001 as per* (b) (4) *The previous validation work has also shown that* (b) (4) *ingress is comparable regardless of the content of vials of the same size. The validation parameters will be assessed in line with current ICH Q2R1 guidelines.*

Reviewer Comments to CP

OTAT and DMPQ do not approve of the reduced reporting category of a CBE-30 following successful completion of the CP as the changes proposed constitute major changes. An IR was sent to Bioverativ on February 7, 2023 recommending the reporting category upgraded to a Prior Approval Supplement (PAS) following successful completion of the CP. Bioverativ responded to the IR on February 10, 2023 (STN 125771/0.34) acknowledging the reporting category change to a PAS.

Overall Reviewer's Assessment of Comparability Protocol Section:

- The proposed comparability protocol appears acceptable as DP manufactured at (b) (4) will be compared to that manufactured at (b) (4). Although (b) (4) (b) (4) has an acceptable FDA inspection history there have been no FDA-led inspections since (b) (4) (b) (4) rooms are new to the BIVV001 manufacturing process, the (b) (4) room (not classified) and f(b) (4) room (b) (4) In addition, a (b) (4) will be introduced to the DP process, (b) (4) lyophilizers, and (b) (4) CCIT methodology. Depending on timing and results of the PPQ studies an inspection of the (b) (4) facility may be warranted prior to approval of the CP. Therefore, DMPQ agrees that the appropriate reporting category following successful completion of the CP should be a Pre-Approval Supplement (PAS) as an inspection of the facility may be necessary.